RESEARCH ARTICLE

Development of Vaginal Tablet of Clotrimazole Prepared by Applying the Concept of *Percolatio* Threshold

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ABSTRACT

Clotrimazole is the drug of choice in the treatment of vulvovaginal candidiasis and belongs to biopharmaceutical classification system (BCS) class IIb. Therefore, it should be presented in appropriate form adopting a suitable formulation approach to ensure its fast and complete release in the vagina. Solid dispersion of clotrimazole was prepared using microcrystalline cellulose as a carrier material after confirming their miscibility into each other by the 'melting point depression' method. Vaginal tablets of the solid dispersion of clotrimazole were prepared by direct compression using co-processed crospovidone as a novel disintegrant (1.5% w/w) to ensure fast disintegration of the tablet. Co-processed crospovidone was selected as a novel disintegrant and its proportion in the formulation was decided by applying the concept of percolation threshold. The superior functionality of co-processed crospovidone as a disintegrant was because of its larger pore size i. e., 4.27A^o than the pore size of crospovidone 3.99A^o. The faster ingress of water through the larger pores leads to the fast disintegration of the tablet. Rapid release of the drug from the disintegrated tablet dosage form was confirmed by performing *in-vitro* antifungal studies. The statistical analysis of the data obtained after applying the student 't' test indicated that there was a difference in the means of zone of inhibitions between the tablets of optimized composition and the tablets the plain clotrimazole at $p<0.5$.

Keywords: Co-processed crospovidone, *Percolation* threshold, Vaginal tablet, Fast disintegration.

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INTRODUCTION

Clotrimazole is the drug of choice in the treatment of vulvovaginal candidiasis and belongs to biopharmaceutical classification system (BCS) Class IIb i.e. it is a poorly soluble drug.[1] Therefore it would be incompletely released/ absorbed at an application site unless presented appropriately by adopting suitable formulation approach.[2] In comparison with novel vaginal drug delivery systems, conventional vaginal tablets enjoy certain advantages such as better patient compliance (due to lesser physical discomfort) and easy processing.[3] It is proved in the previous studies that, the release of the drug from the vaginal tablet formulation is well correlated with the disintegration of the tablet. Fast disintegration of the vaginal tablet leads to fast release of the drug and the fast release of the drug is required for fast diffusion of the drug through vaginal mucosa. Thus the fast disintegration of the vaginal tablets is the first step in their therapeutic success.[4]

The percolation threshold model had been used successfully to explain the disintegration performance of the formulations containing various drug loadings and different disintegrants.[5] Solid dispersion of clotrimazole was prepared by using microcrystalline cellulose PH102 (MCC) as a carrier. This carrier was selected on the basis of a drug-carrier miscibility study and was confirmed by the 'melting point depression' method.[6] The tablets of solid dispersion of clotrimazole were prepared by using two different disintegrating agents, such as crospovidone and co-processed crospovidone.

Disintegration is always initiated by the ingress of the disintegration medium through the pores of the tablet and it happens at the percolation threshold. Percolation theory is a well-researched tool for the design and development of tablets as a pharmaceutical dosage form. The type and the proportion of disintegrant in the vaginal tablet formulation of solid dispersion of clotrimazole were decided by following a mathematical approach based on percolation theory. The wetting constant K changed abruptly at 2.75% w/w of crospovidone and at 1.5% w/w of co-processed crospovidone in tablet formulations. This indicated that the clusters were formed at these levels and were thus the percolation thresholds of these disintegrating agents respectively.[7]

The lesser percolation threshold of the co-processed crospovidone depicts its superior functionality as a disintegrant

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than crospovidone.[8] Hence, the *in-vitro* antifungal study of the tablet compositions containing co-processed crospovidone as a disintegrating agent was performed against *Candida albicans*.[9] The experimental data was analyzed by applying student's 't' test. The zone of inhibition of the tablet of a composition containing co-processed crospovidone (1.5% w/w) was larger (at $p < 0.5$) than the zone of inhibition of the tablet of physical mixture of the equivalent amount of clotrimazole, MCC and crospovidone. Thus, it was concluded that the inclusion of co-processed crospovidone as a novel disintegrating agent as well as the selection of microcrystalline cellulose PH102 (MCC) as a carrier in the solid dispersion of clotrimazole promoted faster disintegration of the tablet followed by the faster release of clotrimazole.

MATERIALS AND METHODS

Clotrimazole was gifted by Lupin Research Park, Pune, and microcrystalline cellulose PH102 (MCC), and crospovidone were received as gift samples from Mylan Laboratories, Aurangabad. The seeds of *Ocimum basillicum* were purchased from the local market and were authenticated from the Agharkar Research Institute, Pune. Other chemicals used in the formulation were of pharmaceutical grade and the chemicals used in the analysis were of analytical grade and were used as received.

Selection of Suitable Carrier for the Preparation of Solid Dispersion of Clotrimazole

Physical mixtures of clotrimazole in microcrystalline cellulose PH102 (MCC) were prepared in proportions as 40, 60, and 80% w/w by gentle mixing using mortar and pestle. Sample of 2 to 4 mg of each mixture was then analyzed by differential scanning calorimetry at a heating rate of 10°C/min from 30 to 300°C to determine the onset of the melting point.[6]

Preparation of Solid Dispersion of Clotrimazole

Solid dispersion of clotrimazole (CLO) in microcrystalline cellulose PH102 (MCC) was prepared by kneading method.[10-12] Acetone was added to MCC to prepare its thick slurry. The drug was completely dissolved in acetone. These mixtures were mixed together with continuous stirring using a mechanical stirrer at 450 rpm. The solid dispersion was obtained by evaporating the solvent until it completely dried. The proportion of the CLO: MCC was 1:8 in the solid dispersion form. The content uniformity of the solid dispersion was determined before proceeding for the preparation of the vaginal tablets.

Preparation of Two Sets of Vaginal Tablet Formulations of Solid Dispersion of Clotrimazole

One set of the tablet formulations of solid dispersion of clotrimazole were prepared by using only crospovidone as disintegrating agent in various proportions as 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, and 5%. One more set of the tablet formulations of solid dispersion of clotrimazole were prepared by using co-processed crospovidone as a disintegrating agent in various proportions as 1, 1.5, 2, 2.5, and 3%. The solid dispersion of clotrimazole and crospovidone or co-processed crospovidone (in all the proportions mentioned earlier) was sifted through mesh 20. Each mixture was mixed thoroughly for 5 minutes in a polythene bag. The required amount of magnesium stearate was sifted through mesh 20 and mixed with the above blend for 3 minutes. The bulk properties for all the compositions were measured and the tablets of each composition were prepared by compressing the blend on rotary tablet machine (Cad-Mech) using B -tooling (18.90 × 9.80 cm).

The Water Uptake Study for the Selection of the Type and the Proportion of the Disintegrating Agent

Quantitative analysis of water penetration and uptake into the tablets was performed by using 1% w/w methylene blue dye solution. One tablet belonging to each composition was kept in a clean and dry pre-weighed petri plate (W_1). In 10 mL of dye solution was added carefully in the petri plate and wetting time of the tablet (t) was measured. Excess of dye solution was immediately but carefully removed/decanted from the petri plate after complete wetting of the tablet. Weight of swollen tablet along with petri - plate was noted (W_2). This process was repeated in triplicate for tablets of each composition. Amount of water uptake was calculated by difference in weights as [$M(t) = W_2 - W_1$]. The average kinetic constant of water uptake (K) value for the three tablets of each composition was calculated by the equation,

$$M(t) = K \times \sqrt{t}. \text{ --------Eq.}^{n} 1.$$

Where, where M (t) = amount of water uptake; t = wetting time; K =kinetic constant of water uptake. The graph of the kinetic constant of water uptake versus disintegrant content was plotted for all the compositions containing crospovidone and co-processed crospovidone separately.[7,13] The percolation thresholds were determined after analyzing the graphs.

Optimization of Vaginal Tablet of Solid Dispersion of Clotrimazole

The compositions of the vaginal tablets of the solid dispersion of clotrimazole for optimization were decided considering the percolation thresholds of two different disintegrating agents. The compositions of all these formulations are given in Table 1. Tablets of all these compositions were prepared by the same process mentioned in the earlier section.

A disintegration study was performed by observing the disintegration of six tablets of each composition using the disintegration test apparatus. Distilled water was used as a disintegrating medium and the study was conducted at 37 ± 2°C. The data generated after the disintegration time study of the formulations was analyzed by applying the Student's 't' test.[14] The formulation that exhibited minimum disintegration time was selected as an optimized formulation.

In-vitro Antifungal Study of the Optimized Formulation

In-vitro clotrimazole release study of the optimized formulation was assessed on the basis of the results of *in-vitro* antifungal study. The antifungal activity study was performed *in-vitro* against *Candida albicans* using 'bore well diffusion method'. The *C. albicans* strain was grown on the sabouraud dextrose agar medium at 37°C. Then, a single isolated colony was

Table 1: Composition of vaginal tablets of solid dispersion of clotrimazole

Ingredients in mg/ Tablet Formulation code	*Solid dispersion equivalent to 100 mg clotrimazole*	*Crospovidone*	*Co-processed crospovidone*	*Magnesium stearate (2%)*
V1	900	22.5 (2.5%)	--	18.45
V2	900	24.75 (2.75%)	--	18.5
V3	900	--	13.5 (1.5%)	18.27
V4	900	--	18 (2%)	18.36

suspended in a sterile sabouraud dextrose broth to prepare a fungal suspension. Sterile petri dishes were seeded with 100 µL of the microorganism suspension and then a specified amount of the molten sabouraud dextrose agar medium (45–50°C) was poured into the seeded petri dishes to give a depth of 3 to 4 mm and allowed to solidify. A sterile oval borer was used to remove oval plugs of appropriate dimension from the agar; so that the tablet can be put into the bore conveniently. The positive control in the study was tablet containing a physical mixture of clotrimazole and MCC instead of the amount of solid dispersion and a placebo tablet of equivalent composition without clotrimazole was used as a negative control. Tablets of the three different compositions (Formulation V3, positive control and negative control) were put into the oval wells in triplicate. The seeded plates were incubated at 37°C for 48 hours, and then the average diameters of the inhibition zones were measured in centimeters.[9, 15]

RESULTS AND DISCUSSION

Selection of Suitable Carrier for the Preparation of Solid Dispersion of Clotrimazole

Molecular or nearly molecular dispersion of drug in a carrier is called as solid dispersion. Recrystallization or aggregation of dispersed drug in a solid dispersion form during shelf life is always the point of major concern in its commercial success. It can be minimized or prevented if the carrier is selected properly. The physical stability of a drug in its solid dispersion form (i.e., distribution of the drug in a carrier without re-aggregation) also depends on its glass-forming ability. Clotrimazole belongs to class 3 of glass-forming drugs. Such drug candidates are the most suitable candidates for the adaption of solid dispersion as a formulation approach. If drug is soluble/miscible with the selected carrier in such cases, the solid dispersions are stable even at the highest drug loading.[16] If the polymeric material has glass transition temperature (Tg) lesser (by at least 20ºC) than the drug's melting point then, the 'melting point depression method' is the method of choice to confirm their miscibility. MCC PH102 has its glass Tg at 126.32ºC and the melting point of the clotrimazole is at 148 to 151ºC. Therefore, it was selected as a carrier in the present study. The overlay of DSC thermo-grams of the physical mixtures of CLO-MCC is shown in Figure 1. The onset of the melting of clotrimazole decreased with an increase in the MCC content in physical mixtures. It confirmed the miscibility of clotrimazole in MCC PH102.[6]

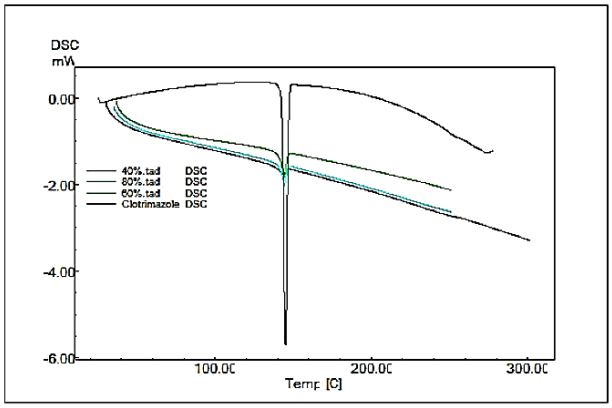

Figure 1: Overlay of thermographs of physical mixtures of CLO: MCC

Preparation of Solid Dispersion of Clotrimazole

The solid dispersion of clotrimazole in microcrystalline cellulose PH102 was white, odorless, and free-flowing (with angle of repose 27.3º). The uniformity of content was determined by assay method and was 100.3% w/w. The compressibility Index was excellent (7.14%).

Preparation of Two Sets of Vaginal Tablet Formulations of Solid Dispersion of Clotrimazole

The bulk properties of the blends of all the compositions (solid dispersion with crospovidone or co-processed crospovidone in various proportions) described earlier were within acceptable limits and thus were suitable for direct compression.[17] The water uptake study was performed using three tablets of each composition.

The Water Uptake Study for the Selection of the Disintegrating Agent

The water uptake study was performed to select the disintegrating agent and its appropriate proportion by applying the concept of the percolation theory. The percolation threshold is purely mathematical concept that describes the formation of clusters, i.e., long-range connectivity of any one component in random systems. At the percolation threshold, i.e., at some particular concentration of one component (disintegrant); some property of a system changes abruptly (e.g. wetting time of the tablet in the present study) or suddenly becomes evident. Below the percolation threshold, a cluster does not exist. The water uptake constants were calculated and plotted against the disintegrant content in percent to determine the percolation thresholds of the crospovidone and co-processed crospovidone in the tablet formulation.[18] This constant increased gradually with the disintegrant content up to the percolation threshold value and then decreased (Table 2). This was due to the

hindered ingress of dye solution into the tablet formulation as a function of the extent of the swelling of the disintegrant in proportion to its amount present in the tablet.[7] The percolation threshold of crospovidone in the tablet of the solid dispersion of the clotrimazole (SD) was between 2.5 and 2.75% and of co-processed crospovidone was between 1.5 and 2% (Figures 2 and 3).

Optimization of Vaginal Tablet of Solid Dispersion of Clotrimazole

Disintegration of the tablet is a cumulative result of many interdependent mechanisms taking place; when the tablet is put into the disintegrating medium. These include ingress of disintegrating medium into the water, wetting of clusters of the disintegrating agent distributed in the tablet structure and the response of the disintegrating agent to the medium by swelling or deformation or wicking or repulsion.[7,19] When the tablet comes in contact with the aqueous disintegration medium, the disintegration medium penetrates the tablet through the pores present in the microstructure of the tablet. This is a wicking action.[20,21] Crospovidone exhibits this as predominant mechanism of its disintegration.[22] Hydrogel isolated from the seeds of *Ocimum basilicum* is reported as a disintegrating agent.[23] It is also reported to possess very high swelling index. Wicking and swelling are the most acceptable mechanisms of tablet disintegration and hence be well balanced in functional disintegrating agent.[24] Thus, uptake of the disintegrating medium into the tablet (wicking) followed by the swelling of the disintegrant added are the prerequisites for efficient/ faster tablet disintegration.[13] It was envisaged in the present work that co-processing of crospovidone with the hydrogel isolated from the seeds of *O. basilicum Ocimum basilicum* would yield co-processed material with improved disintegrant functionality.[25-27]

The average pore radius of the co-processed crospovidone was 4.27A^{o} and was more than the average pore radius of the crospovidone (3.99A^{o}). The faster ingress of the disintegrating medium in the tablet containing co-processed crospovidone was the cumulative effect of the wicking action of crospovidone, swelling tendency of the hydrogel isolated from the seeds of *O. basilicum* and more average pore radius of the co-processed crospovidone.[8, 28] The disintegration time of this formulation (V3) was also least among all the tablet formulations. This inference could further be justified on the basis of wetting time also. Disintegration time is one of the important parameters to ensure therapeutic efficacy of the vaginal tablet of clotrimazole. The type and the concentration of the disintegrating agent have the highest influence on the disintegration time.[29] The analysis of the disintegration time data (after applying student's 't' test to compare means of two different samples) clearly indicated that there is statistically significant difference in the disintegration time (tablets of composition V2 and V3) at $p < 0.005$ when two different disintegrating agents were used in the composition. Therefore, the formulation of the composition V3 was selected as an optimized composition.

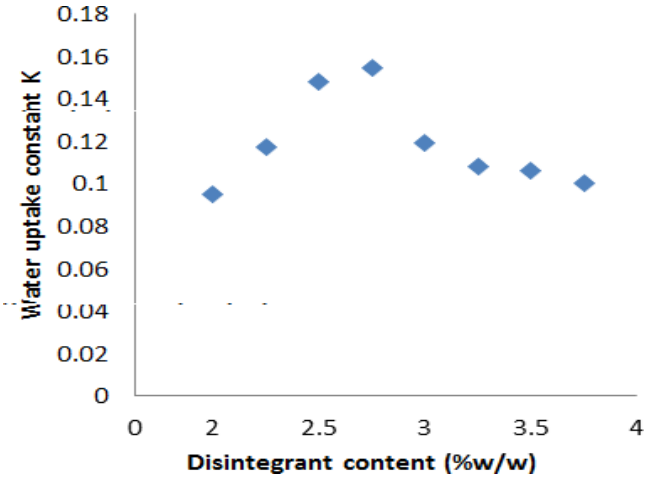

Figure 2: Water uptake constant K of the binary systems of SD/ Crospovidone

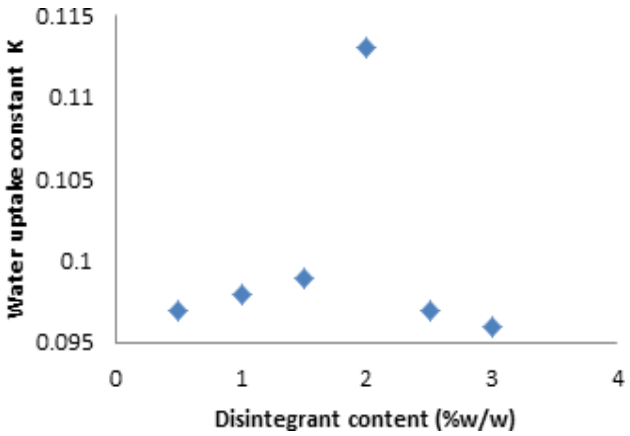

Figure 3: Water uptake constant K of the binary systems of SD/Co-processed crospovidone

Table 2: Data for application of the percolation theory

Crospovidone	*2%*	*2.25%*	*2.5%*	*2.75%*	*3%*	*3.25%*	*3.5%*
K	0.095	0.117	0.148	0.154	0.119	0.108	0.106
Wetting time (sec)	49.07	31.84	24.06	23.38	26.14	31.15	32.38
D T (min-sec)	--	--	4	--	--	--	--
Co-processed crospovidone	*0.5%*	*1%*	*1.5%*	*2%*	*2.5%*	*3%*	
K	0.097	0.098	0.099	0.113	0.097	0.096	
Wetting time (sec)	42.32	40.20	26.66	27.56	35.21	34.85	
D T (min-sec)	--	--	1.28	1.54	--	--	

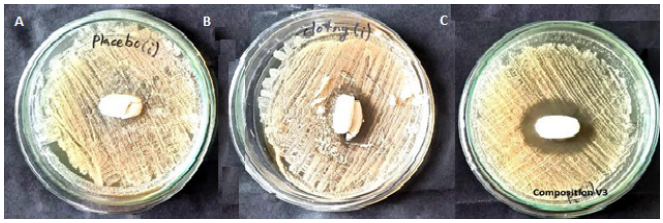

Figure 4: *In-vitro* antifungal study; A: Negative control, B: Positive control, C: Optimized formulation

In-vitro Antifungal Study of the Optimized Formulation

The zones of inhibition were measured after 24 hours (Figure 4) and statistically analyzed. After statistical analysis, it was concluded that the formulation of composition V3 (optimized formulation) had significantly larger zone of inhibition than the zone of inhibition obtained for the tablet of the physical mixture of clotrimazole, MCC and co-processed crospovidone. The larger zone of inhibition for the tablet of composition V3 might be attributed to the fast disintegration of the tablet of composition V3 as well as miscibility of clotrimazole with the carrier.[30, 31] The fast disintegration of the tablet of optimized composition resulted in fast release and proportionate faster diffusion of the drug into the agar. Since, the experimental conditions and the amount of drug present in the dosage forms were same, the size of zone of inhibition in the present work was a function of radial diffusion of the released drug from the dosage form.[32] The statistical analysis of the data after applying Student 't' test indicated that there was difference in the means of zone of inhibitions between the tablet of composition V3 and suspension of the clotrimazole at $p < 0.5$.

CONCLUSION

Solid dispersion is promising formulation strategy for poorly soluble drugs. If the carrier material is selected appropriately in which the poorly soluble drug is miscible; it lowers the molecular mobility of the drug in the solid dispersion form and hence its ability to nucleate and recrystallize. Microcrystalline cellulose PH102 was selected as a carrier material to prepare the solid dispersion of clotrimazole. The 'melting point depression method' was used to confirm the solubility/miscibility of clotrimazole in MCC PH 102. The vaginal tablets of solid dispersion of clotrimazole were prepared by direct compression using co-processed crospovidone as a novel disintegrating agent. Co-processed crospovidone was selected as the suitable disintegrant in the present work by applying the concept of percolation threshold. The faster release and hence faster diffusion of the clotrimazole into the surrounding medium from the optimized formulation was confirmed by performing *in-vitro* antifungal studies. Thus, the present study established the algorithm for the development of the vaginal tablet dosage form of the poorly soluble drug; that ensures faster release of poorly soluble drug from the tablet dosage form.

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